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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,579	03/22/2002	Lou Franciscus M. H. De Leij	05032-00098	1723

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EXAMINER
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QIAN, CELINE X

ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 09/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/009,579

Applicant(s)

DE LEIJ ET AL.

Examiner

Celine X. Qian Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 05 September 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1,2,4-9,14,20,21 and 24 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,2,4-9,14,20,21 and 24 is/are rejected.
- 7) ☒ Claim(s) 5 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 30 October 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

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### **DETAILED ACTION**

Claims 1, 2, 4-9, 14, 20, 21 and 24 are pending in the application.

This Office Action is in response to the Amendment filed on 9/5/06.

#### ***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/5/06 has been entered.

#### ***Response to Amendment***

The rejection of claims 1, 2, 4-9, 14, 20, 21 and 24 under 35 U.S.C. 112 1<sup>st</sup> paragraph is maintained for reason set forth of the record mailed on 5/15/06 and further discussed below.

#### ***Response to Arguments***

#### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-9, 14, 20, 21 and 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

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application was filed, had possession of the claimed invention. Claims 20, 21 and 24 are included because the dependency of the claims are amended.

In response to this rejection, Applicants argue that the amended claim 1 now recites structural feature that at least three Ets binding sites and at least one Sp-1 binding site are present in the claimed promoter region. Applicants assert that this claimed structural feature correlates with the claimed function of allowing expression of a nucleic acid of interest operably linked to the promoter in a cancer cell in an epithelial selective manner. Applicants assert that the claimed nucleic acid sequence having the claimed binding sites are capable of mediating epithelial specific expression. Furthermore, Applicants assert that the binding sites are well known in the art for having regulative function of transcriptional activation in an epithelial specific manner as disclosed in the instant specification. Applicants also cite Berg et al., Macleod et al., Lania et al and Suske et al. to describe Ets and Sp-1 transcription factors and their DNA binding regions. Applicants further argue that tissue specific expression is not conferred by stretches of hundreds of nucleotides per se, but by the presence of combinations of short cis acting sequence capable of binding transcription factors. Moreover, Applicants assert that the instant specification provides protocols that may be used to determine whether a claimed nucleic acid sequence functions to mediate expression of a nucleic acid of interest in an epithelial specific manner. Applicants thus conclude that the written description requirement is met.

The above arguments have been fully considered but deemed unpersuasive. The reasons for the written description rejection were discussed in detail in the office actions mailed on 1/25/05 and 5/15/06. In response to Applicant's argument, Applicant is

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reminded the guideline of written description as set forth in MPEP 2163R-2. It states:

“The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.” In the instant case, Applicants admit in the response filed on 2/1/06 (see page 6, 3<sup>rd</sup> paragraph) that the specification does not provide a description of the structural and functional definition of a functional equivalent of a nucleic acid sequence having the sequence from 3200 to 3556 of SEQ ID NO:5. According the guideline set forth in MPEP and cited above, description of an assay that makes or identifies the claimed invention alone does not constitute sufficient description of the claimed invention without structural and functional relationship.

In response to Applicant’s argument with regard to the presence of putative binding sites of Ets and Sp1, Applicants are reminded the mere presence of said binding sites within the claimed sequence does not indicate that the claimed sequence can direct epithelial specific transcription. Contrary to Applicant’s assertion, the mere presence of putative binding site of Ets and Sp-1 does not necessary result in epithelial specific expression. The specification cites Lee et al. to demonstrate that the combined interaction of Ets and Sp-1 is known to regulate epithelial specific expression. However, this does not mean that the presence of Ets and a proximal Sp-1 binding site is sufficient

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for regulate epithelial specific expression. Lee et al. disclose the proximal promoter of the human transglutaminase 3 gene is highly active in keratinocyte NHEK cells. Lee et al. further disclose that the binding of Sp-1 and Ets to the promoter sequence by gel mobility shift assay. Lee et al. conclude that the cooperative interaction between Ets and Sp-1 in the proximal TGM3 gene promoter region involves not only Sp-1, but also additional unidentified nuclear proteins in the NHEK nuclear extracts (see page 4567, 2<sup>nd</sup> col., 2<sup>nd</sup> paragraph). A review of exhibit A-D does not support the notion that the presence of Ets or Ets and Sp-1 putative binding site within the 5' untranslated region of GA733-2 is sufficient for direct epithelial specific expression. Macleod et al. disclose that Ets-1 is expressed in thymus and endothelial cells (see table 1), whereas Suske et al. and Lania et al. disclose Sp1 is expressed ubiquitously (see table 1 of both articles). Berg discusses binding sites for Sp1 and sub-family of zinc finger proteins, which does not address whether the presence of this protein renders any promoter to direct expression in an epithelial specific manner. As such, none of the cited art illustrates that the mere presence of the putative binding site Ets and Sp-1 within a promoter region would confer epithelial specific expression. The specification only teaches a 4.2 kb region at 5' of the GA733-2 gene and several fragments within this region that confers expression in SW948, an adenocarcinoma, and COS-7, but not in FLF (human fetal lung fibroblast) and HUVEC (human umbilical veins). The specification does not teach whether the claimed region of 356 bp confer epithelial specific expression although Ets and Sp1 binding sites are presented in this region. The specification also fails to teach regulatory regions of other genes of "functional equivalent" thereof that have claimed function of being epithelial selective. The presence of the short cis-acting region is important for tissue

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specific expression, however, it is the collective interaction of all transcription factor within the promoter region directs tissue specific expression. As such, other factors such as the distance between the various putative binding site is also important for such interaction. The mere presence of Ets and Sp1 putative binding site within the claimed nucleic acid sequence is not sufficient structurally for the claimed function. Absent evidence from the contrary, the specification fail to describe a representative number of species by their complete structure and other identifying characteristics to satisfy the genus claim. Therefore, this rejection is maintained.

Claim 14 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In response to this rejection, Applicants argue that the amended claim is directed to a medicament for treating epithelial cancer includes an isolated or recombinant nucleic acid sequence according to claim 1 and a suicide gene. Applicants argue that the use of known suicide genes such as TK with the promoter enables the claimed medicament because such practice is known in the art at the time of filing. Applicants cites Springer and Niculescu-Duvaz to demonstrate that gene therapy using suicide genes was being used in more than 25 clinical trials at the time the article was published. Applicants further assert that immune response is not a problem to gene therapy but rather increases the efficacy of gene therapy. Applicants thus conclude that claim is enabled.

The above arguments have been fully considered but deemed unpersuasive. The examiner reiterates that the state of art at the time of filing regard the success of gene

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therapy as unpredictable (see detailed discussion in previous office actions). The citation provided by Applicants, Springer and Niculescu-Duvaz further supports this notion. This references teaches “some hurdles must be overcome before GDEPT will become a clinically efficient treatment of cancers (see page 1166, 1<sup>st</sup> col., 3<sup>rd</sup> paragraph, 1<sup>st</sup> sentence).” The authors went on to discuss such hurdle including major improvement on vector design to enhance targeting and delivery of suicide gene, which is same as what is discussed in Verma et al. (cited previously). The testing in clinical trials does not mean the treatment is effective. Contrary to Applicant’s assertion, the instant specification does not provide any in vitro or in vivo data that demonstrates the medicament as claimed is effective in treating epithelial cancer. Thus, for reasons set forth in the previous office actions and above, the claimed medicament is not enabled.

### ***New Grounds of Rejection***

#### ***Specification***

The specification is objected to for following reasons (sequence in Figure 1 has no sequence identifier and no brief description of the drawing).

#### ***Claim Objections***

Claim 5 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 1 already recites a nucleic acid of interest, thus claim 5 fail to limit claim 1.

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***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 24 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claim 24 is rejected under 35 USC §101 because the claimed invention is directed to non-statutory subject matter. The term “host” as defined by the specification at page 9 line 27-29 states that the cell is present or intended to be present in a human being, said cell becoming integrated into the human being and therefore being an inseparable part of the human itself. The scope of the claim, therefore, encompasses a human being, which is non-statutory subject matter. As such, the recitation of the limitation “an isolated or in vitro” would be remedial. See 1077 O.G. 24, April 21, 1987.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 14 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

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The instant specification discloses that the medicament is for treatment of cancer or preferably carcinoma (see page 9, [24]), not for epithelial cancer. Therefore, the newly introduced limitation of treating epithelial cancer constitutes new matter.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X. Qian Ph.D. whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

CELINE QIAN, PH.D.  
PRIMARY EXAMINER



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Art Unit 1636